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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,619	THORSETT ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 35-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 35-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the response filed 7/23/04, no claim has been amended, cancelled or added. Claims 1 and 35-59 remain pending.

✧

Claims 58-59 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-50 and 54 of copending application Serial No. 09/127364, or claims 33-34 of 10/316205. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 48 (of application 09/127364) does not require that the treatment (if and when successful) is effective solely because of VLA-9 anatagonism. In fact, the claims (of 09/127364) do not require that the efficacy of the compound is due in part to antagonism of VLA-9. The claims (of 09/127364) encompass the possibility that the efficacy is due entirely to a mechanism that is independent of VLA-9 antagonism. Moreover, some of the diseases to be treated are the same in the instant application, and the two copending applications. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented]

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d).

✧

Claims 1 and 35 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, variable R^5 is defined. Within that definition, the following denotations are recited: -0-Z-N(R^8)($R^{8'}$) and -0-Z-R^{12}

  In both cases, the character preceding "Z" is a zero; it should be a capital "O".

- In claim 35, variable R^3 is defined. One option for R^3 is recited to be "substituted allcyl". It appears that *alkyl* may be intended, rather than "allcyl".

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-56, 58, 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification states (p. 334, line 29+) that each of the compounds of examples 1-373

exhibited an IC_{50} of 15 μM or less in an assay which endeavors to assess the binding of compounds to α4β1 integrin. From this, applicants are asserting that the compounds will be effective in the treatment of Alzheimer's disease, arthritis AIDS dementia, encephalitis, MS, tissue transplantation, meningitis, and tumor metastasis. However, applicants have provided no evidence that this is the case. While it may be true that α4β1 integrins are peripherally involved in each of these disease states, it is far from clear that a disorder in the binding of integrins is the primary cause of the diseases.

In addition, it is not established that the compounds, if administered, will reach the appropriate anatomical site(s), that they will accumulate to a sufficient extent to be effective

The assertion by the examiner is that (a) structure/activity relationships in VLA-4 antagonism are unpredictable, and (b) treatment of inflammatory conditions is unpredictable as well. Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:

  cyclo[Ile-Leu-Asp-Val-NH $(CH2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)

  These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of $\alpha_4\beta_1$ activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

    - Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_V\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

In addition to the foregoing, the following references teach "failure" in the treatment of one or more inflammatory conditions:

Vatistas N J, "Infection of the intertubercular bursa in horses: four cases (1978-1991)", [*Journal of the American Veterinary Medical Association* **208** (9) 1434-7, 1996];

Tait A, "Synthesis and antiinflammatory activity of 2,6-bis(1,1- dimethylethyl) phenol derivatives" (*Farmaco* **48** (10) 1463-73, 1993);

Kurokawa M "Synthesis and antiinflammatory activity of cis- and trans- 6,6a, 7,8,9,10,10a,11- octahydro-11-oxodibenzo[b,e]thiepinacetic and -oxepinacetic acids" (*Journal of Medicinal Chemistry* **33** (2) 504-9, 1990);

Uren M F, "The effect of anti-inflammatory agents on the clinical expression of

bovine ephemeral fever" (*Veterinary Microbiology* **19** (2) 99-111, 1989;

Crossley M J, "Studies on the effects of pharmacological agents on antigen-induced arthritis in BALB/c mice" (*Drugs Under Experimental and Clinical Research* **13** (5) 273-7, 1987).

Thus, structure/activity relationships involving VLA-4 are unpredictable. Perhaps it is true that many of the claimed compounds will exhibit an IC_{50} of 15 *micro*molar in an assay of VLA-4. However, the significance of this number (15 μM) with respect to treatment of treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia is unknown. No correlation has been established between this "15 μM" parameter, and successful treatment of any of the foregoing diseases. Moreover, other issues such as bioavailability and pharmacokinetics are not reflected in this "15 μM" number.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident, extrapolation from an observation of VLA-4 binding in vitro to treatment of Alzheimer's disease, AIDS

dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia will produce "unpredictable" results.

In addition to the foregoing, consider the following:

- Pierce, J. W., ("Salicylates inhibit I kappa B-alpha phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration", Journal of Immunology, 156 (10) 3961-9, 1996) discloses that aspirin inhibits ICAM-1 and VCAM-1 expression. In a similar vein, Gonzalez-Alvaro I ("Interference of nonsteroidal antiinflammatory drugs with very late activation antigen 4/vascular cells adhesion molecule 1-mediated lymphocyte-endothelial cell adhesion", Arthritis and Rheumatism 41 (9) 1677-88, 1998) discloses that indomethacin inhibits VLA-4/VCAM-1 interactions. If applicants' assertions were correct, the skilled artisan would predict that success in the treatment of inflammatory conditions would be achieved by any compound which antagonizes VLA-4/VCAM-1 interactions. Yet this is not what one finds. For example, Goldenberg M M ("A pharmacologic analysis of the action of platelet-activating factor in the induction of hindpaw edema in the rat", Prostaglandins 28 (2) 271-8, 1984) discloses that neither indomethacin nor aspirin was effective to inhibit an inflammatory response to paw edema in rats. Similarly, Zuany-Amorim C. (European Journal of Pharmacology 257 (3) 211-6, 1994), discloses that aspirin failed to inhibit inflammatory responses to antigen (e.g., page 214, col 1). These findings of Goldenberg and of Zuany-Amorim support the examiner's contention that one cannot predict success in the treatment of inflammatory diseases merely because one can antagonize VLA-4/VCAM-1 interactions in vitro. As two more examples, Rordorf C "Arthritis in MRL/LPR mice and in collagen II sensitized DBA-1 mice and their use in pharmacology", International Journal of Tissue Reactions 9 (4) 341-7, 1987 discloses that indomethacin was not effective to treat arthritis in an animal model, and Goldlust M B (Agents and Actions 11 (6-7) 729-35, 1981) discloses that aspirin was not effective to treat synovitis in rabbits.

- Theien, B. E. (*Journal of Clinical Investigation* **107** (8) 995-1006, 2001) compared the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced

R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS. Accordingly, one cannot predict success in the treatment of MS based on the propensity of a compound to antagonize VLA-4.

- Saez-Torres I ("Peptide T does not ameliorate experimental autoimmune encephalomyelitis (EAE) in Lewis rats", *Clinical and Experimental Immunology* **121** (1) 151-6, 2000) discloses that it is known in the art that peptide T inhibits T cell activation and cytokine production and function. Saez-Torres studied the ability of peptide T to ameliorate EAE in Lewis rats. Peptide T was administered subcutaneously at different doses and phases of the disease according to several treatment protocols. The authors concluded that peptide T neither prevents nor ameliorates EAE in Lewis rats. This supports the conclusion that one cannot "predict" success in the treatment of inflammatory conditions, even if one is able to inhibit T cell activation and cytokine production. This finding of Saez-Torres is relevant in part because VLA-4 is prominently expressed on circulating T-cells.

The foregoing teachings further support the conclusion that one cannot predict efficacy in the treatment of human disease merely by modulating *alpha* 4/ligand interactions *in vitro*. Clearly, "undue experimentation" would be required to practice the claimed invention. It is suggested that claims 58 and 59 be cancelled, and that the terms "pharmaceutical" and "therapeutically effective" be deleted from the claims.

In response to the foregoing, applicants have made several arguments, beginning with the

argument that the level of skill of potential practitioners is very high. The examiner would agree that the "artisan of ordinary skill" is one who would have had many years experience in designing, carrying out experiments, and interpreting the results. The examiner would go so far as to say that the "artisan of ordinary skill" would be able to reconstruct animal models of arthritis, encephalitis, MS, tissue transplantation, meningitis, tumor metastasis nephritis, myocardial ischemia and IBD, at least to the extent that such animal models have been adequately described in the prior art. For example, by administering arthritogenic T-cell clones or collagen type II to a rat, some symptoms of arthritis can be induced. Administration of streptozotocin induces diabetes. And intraperitoneal injection of $CD4^+$ T-cells specific for myelin basic protein can produce a model of autoimmune encephalomyelitis. The examiner will further stipulate that the "artisan of ordinary skill" would be able to administer the claimed compounds, and to create a list of criteria for evaluating the extent to which (or whether) any benefit accrued to the test animal. But the fact that an immunologist or physiologist could conduct such experiments does not mean that they will be successful. For example, if 1% saline is administered to an animal in which an arthritic state had been induced, is it applicants' position that the mere fact of administration equates with a treatment? If benzene is administered to a tumor-bearing animal, would applicants argue that metastasis would necessarily be mitigated, merely because a compound had been administered? Furthermore, no matter how much

career success a given immunologist or physiologist may have enjoyed, if a given compound is predestined to be ineffective in treating a given disease, no amount of education or skill is going to change that.

Applicants have also argued that the skilled artisan would be able to combine the claimed compounds with pharmaceutically acceptable carriers. This is of course true. But if a therapeutically ineffective compound is combined with a "pharmaceutically acceptable carrier", the result is not going to be a composition which is effective for "pharmaceutical" applications, nor is the resulting composition going to contain a "therapeutically effective amount" of anything.

Next, applicants have commented briefly on the references cited by the examiner. The examiner would actually agree that none of Dutta, Arrhenius, Komoriya, Haworth, Haubner or Yang, taken by themselves, adequately make the case for unpredictability of the proposed extrapolation (i.e., VLA-4 antagonism in vitro → therapeutic success in vivo). However, at some point in the future, applicants may choose to provide one or more journal articles which make the point that some therapeutic benefit may accrue if a monoclonal antibody to VLA-4 is administered to an animal in which a given inflammatory disease state has been induced. Should this event come to pass, one of the arguments made by the examiner will be that VLA-4 antagonism is a question of degree, i.e., there is a continuum of possibilities. Merely because a tenaciously binding compound can induce some

therapeutic benefit does not mean that much weaker antagonists (such as those claimed) will be equally effective, or even perceptively effective. Thus, some of the references (Dutta, Arrhenius, Komoriya, Haworth, Haubner, Yang) will help to underscore that point. In a related vein, applicants have pointed out that all of the compounds referred to in the references (cited by the examiner) are different from those which are claimed. This particular point is correct. But again, if and when applicants start pointing to prior art compounds to support their position that the claimed compounds are therapeutically effective, the examiner will be able to make the same argument, i.e., that the compounds which applicants regard as exemplary are not the same as those claimed. Alternatively, applicants may choose to adhere to the strategy which they have adopted thus far, which is to abstain from even arguing that other VLA-4 antagonists (from the prior art) can be used to treat the inflammatory conditions recited in the instant claims. As long as that is the strategy, the examiner can continue to argue that there is no evidence of record to indicate that, at the time of the invention (8/1/97), the skilled immunologist (or physiologist) would have believed that a given VLA-4 antagonist would be effective to treat even one of the inflammatory diseases that is recited.

Applicants have also argued that "the claims do not recite any limitations related to ... predicting the viability of treatment methods". This particular statement is entirely untrue, however. Just by reciting the term "pharmaceutical composition", applicants are

asserting that the claimed compounds can be used to treat one or more diseases in humans (or other mammals). And claim 59 is quite explicit in reciting diseases which applicants assert can be effectively treated. Thus, "predictability" is absolutely central to the question of whether the skilled artisan can practice the claimed invention.

On pages 1 and 5 of the specification, applicants acknowledge the importance of VLA-4/VCAM-1 binding to induction of the inflammatory response. As noted by Pierce and by Gonzalez-Alvaro, aspirin and indomethacin both inhibit VCAM-1 expression. If applicants assertions were correct, one would expect that by inhibiting VCAM-1 expression, and thereby VLA-4/VCAM-1 binding, the skilled artisan would be able to reliably predict treatment of inflammatory conditions. Yet this is not what one finds. Furthermore, even if it were possible to reliably predict that if a VLA-4 antagonist is effective when administered to a mammal before the onset of symptoms (a point which is certainly not conceded), it would not follow therefrom that the VLA-4 antagonist will be effective when administered after the onset of symptoms, which is the preferred embodiment of claims 58-59.

If applicants believe that they can demonstrate efficacy of the compounds against Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia, and can do so without the expenditure of "undue

experimentation", it is suggested that applicants undertake what they regard as "routine experimentation", and report the results.

Given that absence of any guidance in the specification, the absence of working examples (showing therapeutic efficacy), the nature of the invention, the state of the prior art, the unpredictability of the art, and breadth of the claims (especially claim 58), the skilled artisan would conclude that "undue experimentation" would be required to practice the claimed invention.

✧

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600